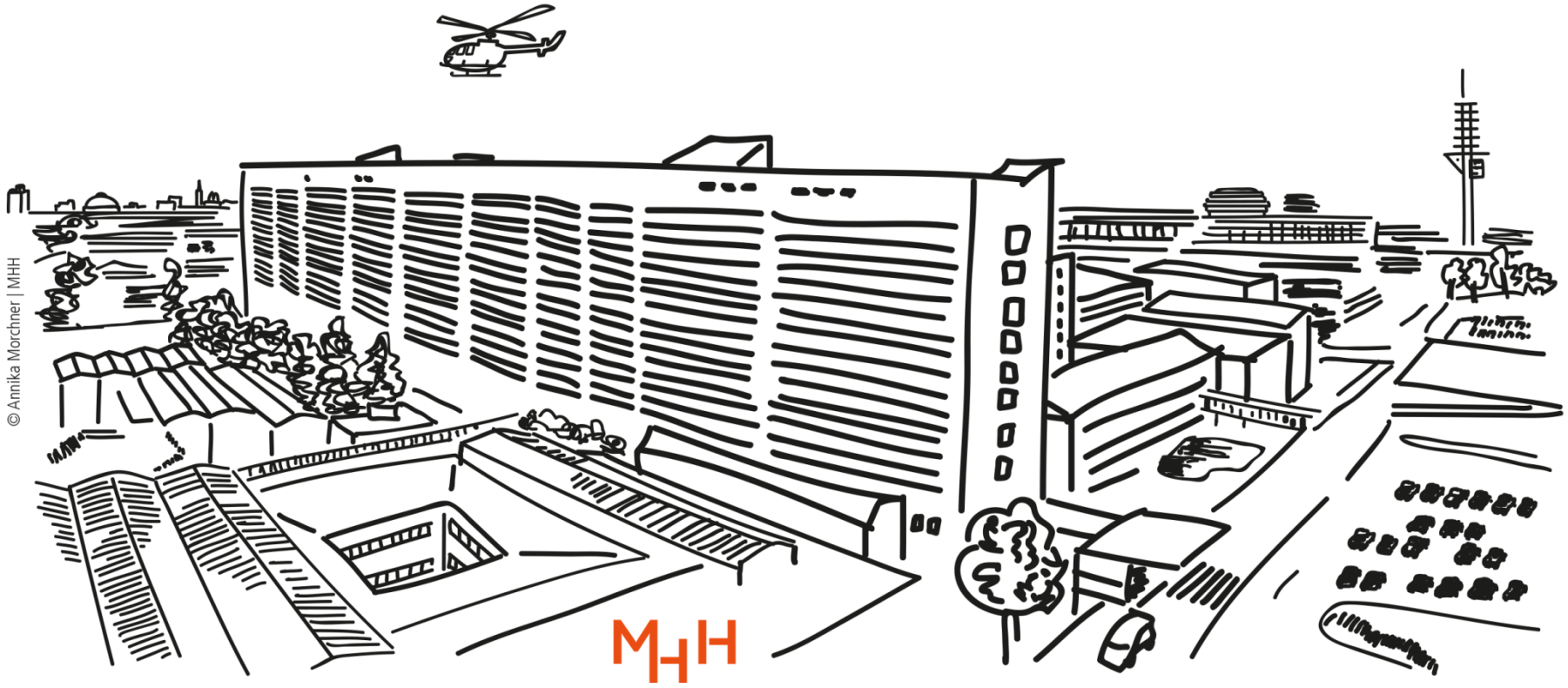
Is there something like „too much innovation “?



Anja Schiel, Armin Koch
SAWP & BSWP

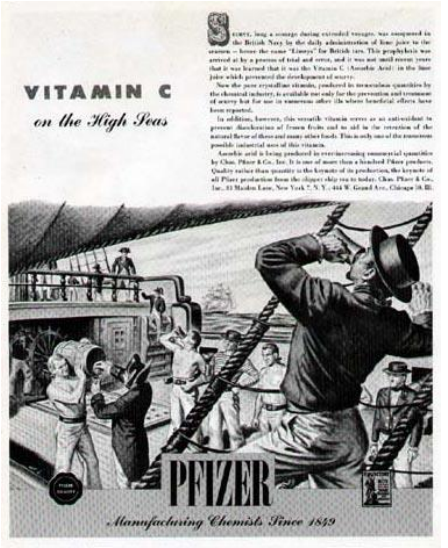
Is there something like „too much innovation “?

Innovation is great (and we made a lot):

(observing, comparing, randomizing, blinding, adapting, not planning (platforming), not randomizing (RWE), observing (BigData))

We discuss (as always) about confirmatory clinical trials:

- early phases are horribly complicated, require in depth knowledge about drugs and mechanisms and what helps, should be done
- after phase II, phase III will follow to confirm (or correct)



https://www.jameslindlibrary.org/

Different perspectives

Discussion with regulators is usually perceived as driven by quite a lot of conservativism, not directly encouraging innovation in experimental design.

Whereas discussion with industry colleagues sometimes is perceived as attempts to stretch innovation in design to the extreme to contribute to the optimization of drug development.

Different perspectives

Discussions end in the magic question:

Do you agree?

… and SAWP (as a multidisciplinary group of experts) is the right place to discuss and search for agreement…

Do you agree?

Agreement presumes:

- A full understanding of the implications
- Experience with the approach
- … or both

Agreement means

- The agreed trial will likely form a sound basis for *proportionate* decision making
- The agreed trial will likely not fail even though the drug is effective (we are experimenting with human beings, not with experiments).✓

Some examples:

The magic of „only 50% of patients will be needed“:

- Implications for the T1E
- Implications for b/r-assessment?
- Implications for the assessment of safety?

The magic of the platform trial:

- Blurring elements of exploration and confirmation
- The role of the comparator and its influence on patient selection

The magic of the (Bayesian) adaptive design:

- see the respective European Reflection Paper: there is a difference between a social event and a confirmatory clinical trial: we need to be able to identify the patients that justify the licensing

Summary:
Is there something like „too much innovation “?

Clearly **NO**

usually there are „Points to Consider“ (and we have to jointly develop them)

… but:

There is something like „too much innovation **at the same time**“ (precisely the point, where we start to experiment with experiments)

Once upon a time ago…

… we discussed an adaptive Phase II/III combo-trial dropping treatment arms, subgroup selection…

In the end “SAWP agreed“ with mentioning all the risks. But also because there were two other, rather conventional phase III trials in the program, so that we thought, that the overall program would be assessable.

New concepts can “sneak” in (in a nice way):

- PROs are sometimes introduced as ~~key~~ secondary's into the confirmatory trials giving opportunity to „familiarize“ with them.
- „beef-up“ information with external controls instead of immediately reducing the amount of trial patients.
- Solve agreed obstacles to trial conduct (sample-size adaptation in depression trials)
- Create win/win-situations (go with two doses into phase III and drop one as soon as it is clear that b/r for the other is better)
- Think other way round: what do we need to know about relevant subgroups?

Respect the idea of parsimonious modelling (… too many modifications question the confirmatory nature of a clinical trial…)

Finis:

In some instances studies can be planned with a so-called adaptive design involving design modifications based on the results of an interim analysis. Such a design has the potential to speed up the process of drug development or can be used to allocate resources more efficiently without lowering scientific and regulatory standards. This is especially welcome if at the same time the basis for regulatory decision-making is improved.

from: Annet Rudolph, Hau-Ruck, arsEdition